

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

75-147

BIOEQUIVALENCE

found to be less than 5%.

In a radiolabeled ISMN study of the drug metabolic fate, about half of the ~~dose~~ dose was eliminated through denitration and renally excreted as isosorbide and sorbitol. One quarter of the dose was accounted for as conjugates of the parent drug in the urine. None of these metabolites is vasoactive. Only 2% of the dose was excreted as unchanged drug.

The overall elimination half-life of ISMN is about 5 hours. About 93% of the radiolabeled ISMN dose was excreted within 48 hours into the urine. Renal excretion was virtually complete after 5 days; fecal excretion amounted to only 1% of the dose. The recommended regimen of ISMN tablets is 20 mg twice daily, with the doses seven hours apart. The most frequent side effect associated with ISMN is headache. Headache decreased in incidence after the first few days of therapy.

ISMN is currently available commercially as Monoket® Tablets, 10 mg and 20 mg, manufactured by Schwarz Pharma.

III. Study Details

A. Study under fasting conditions

Protocol No.	961859
Applicant	Teva, Sellersville, PA
Study sites	Phoenix International, Montreal, Canada
Investigators	Medical Director: Pierre Geoffroy, MD
Study dates	Period 1: 11/24/96 Period 2: 12/8/96
Study design	Open-label, comparative, randomized, single-dose, 2-way crossover bioavailability study.

Subjects Of the 26 healthy, non-smoking, adult male volunteers who enrolled in the study, one did not complete the crossover. Subject No. I elected to withdraw from the study after Period 1 dosing for personal reasons (see Clinical Report for details). Thus, a total of 25 subjects completed the study.

Drug products

1. Isosorbide Mononitrate Tablets (manufactured by Teva Pharmaceutical Industries, Ltd.) 20 mg Batch No. K-20844; Date manufactured: April 14, 1996.
2. Monoket^R (manufactured by Schwarz Pharma AG) 20 mg; Control No. 23743; expiry date: Nov 2000.

Dosing Single oral 1 x 20 mg dose, administered with 240 mL of ambient temperature water. Subjects were dosed while seated and remained seated (or semi-reclined) in bed for the first 2 hours after drug administration.

Food and fluid Subjects were required to fast overnight for at least 10 hours before dosing and for 4 hours thereafter. Water was not permitted for 1 hour before and 1 hour after the dose, but was allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after dosing, and at appropriate times thereafter. Snacks were provided on a regular schedule. During housing, post-dose meal plans were identical for both periods.

Housing From 12 hours before dosing until after the 30-hour blood draw.

Washout Fourteen days between doses.

Blood samples Blood samples were collected pre-dose and at the following times after dosing: 0.167, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 30 hours.

IRB Phoenix International Life Sciences
Institutional Review Board

Informed consent Signed by all subjects.

Assay method for blood samples

Analytes Isosorbide-5-mononitrate (5-ISMN) in plasma.

PK analysis AUCT, AUCI, CMAX, TMAX, KE and THALF were calculated.

Statistical analysis 90% confidence intervals for log-transformed AUCT, AUCI and CMAX were calculated by SAS PROC GLM procedure.

B. Study under fasting/nonfasting conditions

Protocol No. 961860

Applicant Teva, Sellersville, PA

Study sites Phoenix International, Montreal, Canada

Investigators Medical Director: Pierre Geoffroy, MD

Study dates Period 1: 12/21/96
Period 2: 12/28/96
Period 3: 1/4/97

Study design Open-label, comparative, randomized, single-dose, 3-way crossover bioavailability study.

Subjects Of the 18 healthy, non-smoking adult male subjects enrolled in the study, 4 did not complete the crossover.

Drug products

1. Test product under fasting conditions:
Isosorbide Mononitrate Tablets (manufactured by Teva Pharmaceutical Industries, Ltd.) 20 mg
Batch No. K-20844; Date manufactured: April 14, 1996.
2. Test product under nonfasting conditions
Isosorbide Mononitrate Tablets (manufactured by Teva Pharmaceutical Industries, Ltd.) 20 mg
Batch No. K-20844; Date manufactured: April 14, 1996.
3. Reference product under nonfasting conditions: Monoket^R (manufactured by Schwarz Pharma AG) 20 mg; Control No. 23743; expiry date: Nov 2000.

Dosing

Regimen 1: Single oral 1 x 20 mg dose administered with 240 mL of ambient temperature water.

Regimens 2 and 3: Single oral 1 x 20 mg dose administered with 240 mL of ambient temperature water, 30 minutes after a standard breakfast.

All Regimens: Subjects were dosed while seated and remained seated (or semi-reclined) in bed for the first 2 hours after drug administration.

Food and fluid

A standard evening meal was administered at least 10 hours prior to all dosing regimens.

Regimen 1: Subjects fasted overnight for at least 10 hours before dosing and for 4 hours thereafter.

Regimens 2 and 3: Subjects fasted overnight for at least 9.5 instead of 10 hours until 30 minutes prior to their scheduled dosing times, when they were given a standard breakfast.

All Regimens: Water was not permitted for 1 hour before and 1 hour after dosing, but was allowed at all other times. Standard meals were provided at 4 and approximately 9 hours after drug administration and at appropriate times thereafter. During housing, meal plans (at 4 and 9 hours post-dose) were identical for all periods.

Housing

From 12 hours before dosing until after the 30-hour blood draw.

Washout

Seven days between doses.

Blood samples

Blood samples were collected pre-dose and at the following times after dosing: 0.167, 0.25, 0.33, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 30 hours.

IRB

Phoenix International Life Sciences
Institutional Review Board

Informed consent

Signed by all subjects.

Assay method for blood samples**Analytes**

Isosorbide-5-mononitrate (5-ISMN) in plasma.

PK analysis AUCT, AUCI, CMAX, TMAX, KE and THALF were calculated.

Statistical analysis Test/reference ratios for log-transformed AUCT, AUCI and CMAX were calculated.

IV. Analytical Method Validation

A. Pre-study validation

1. Selectivity: No significant interference at the retention time of 5-ISMN or 2-ISMN (internal standard) was observed from endogenous components in blank plasma pools screened.
2. Sensitivity: 3.98 ng/mL for 5-ISMN (7.99 ng for the extended range).
3. Linearity: Linear with a weight of 1/concentration. The correlation coefficients for the standard curves were \geq 0.9964 (0.9970 for the extended range).
4. Precision and accuracy: Between-batch precision and accuracy for QC samples were summarized in Table IV-A-1. Within-batch precision and accuracy for QC samples were summarized in Table IV-A-2. Data in both tables are acceptable.

Table IV-A-1. Between-Batch Precision and Accuracy
of QC Samples

Nominal Conc, ng/mL	N	Accuracy %Found	Precision %CV
10.05	9	101.3	4.9
100.5	10	102	7.4
301.5	11	108.4	6.2
4.02	10	116.3	11.8
20.14	8	108.7	7.3
201.4	8	112	11.6
483.36	8	101.2	6.2
8.06	8	104	12.3

Table IV-A-2. Within-Batch Precision and Accuracy
of QC Samples

Nominal Conc, ng/mL	N	Accuracy %Found	Precision %CV
10.07	10	93.9	7.5
100.7	10	106.6	6.2
302.1	10	104.8	3.7
4.03	10	100	10.2
20.14	10	101.7	10.3
201.4	10	87.6	11.7
483.36	10	101.9	9.2
8.06	10	113.3	5.5

5. Recovery: Mean percent recoveries of 5-ISMN and 2-ISMN were summarized in Table IV-A-3. Recovery data are acceptable.

Table IV-A-3. Recovery Data
for 5-ISMN in Human Plasma

Analyte	Nominal Conc, ng/mL	N	%Recovery	%CV
5-ISMN	10.05	9	99.44	2.0
5-ISMN	100.5	10	101	2.9
5-ISMN	301.5	10	101.3	3.0
2-ISMN	202.16	10	68.9	4.2

6. Stability data: Stability data were summarized in Table IV-A-4. Stability data are acceptable.

Table IV-A-4. Summary of Stability Data

Analyte	Matrix	Conc, ng/mL	N	Storage Condi- tion	Storage Time	% Found	%CV
5-ISMN	Plasma	10.05	10	-22°C	183 days	87.9	10.9
5-ISMN	Plasma	301.5	9	-22°C	183 days	96.6	10.1
5-ISMN	Plasma	10.05	10	20°C	14.8 hrs	96	13.3
5-ISMN	Plasma	301.5	10	20°C	14.8 hrs	96.5	9.6
5-ISMN	Plasma	10.05	10	freeze- thaw	3 cycles	101	7.9
5-ISMN	Plasma	301.5	10	freeze- thaw	3 cycles	101.4	6.6
5-ISMN	Solvent	10.07		auto- sampler @20°C	8 hrs	89.1	

5-ISMN	Solvent	100.7		auto-sampler @20°C	8 hrs	93.6	
5-ISMN	Solvent	302.1		auto-sampler @20°C	8 hrs	97.5	
5-ISMN stock solution	methanol	10.05 mcg/mL	10	-22°C	176 days	104.4	4.8
2-ISMN stock solution	methanol	10.02 mcg/mL	10	-22°C	180 days	99.4	7.9
5-ISMN	Solvent	10.05	10	Extract stabi- lity @20°C	27.2 hrs	95.0	4.4
5-ISMN	Solvent	302.5	10	Extract stabi- lity @20°C	27.2 hrs	97.2	5.2

B. Within-study validation

Precision and accuracy data for the calibration standards and quality control samples for the studies under fasting conditions and nonfasting conditions were summarized below.

1. Study under fasting conditions

- a. Calibration standard concentrations:** Back calculated calibration curve data for 5-ISMN are shown in Table IV-B-1. Data are acceptable.

Table IV-B-1. Back Calculated Calibration Curves
5-ISMN

Nominal Conc, ng/mL	N	%Nominal	%CV
7.99	18	93.7	11.7
15.98	20	99.1	9.9
29.97	20	103.1	9.3
89.91	15	105.6	8.6
299.7	21	100.3	6.2
449.55	20	100.2	5.4
539.46	20	98.2	5.6
599.4	21	100.6	6.1

- b. Quality control samples: Precision and accuracy for the QC samples are shown in Table IV-B-2. Data are acceptable.

Table IV-B-2. Precision and Accuracy for QC Samples

Nominal Conc, ng/mL	N	%Nominal	%CV
20.14	42	109.2	12.7
201.40	42	107.3	6.7
483.36	40	103.9	9.5

2. Study under nonfasting conditions

- a. Calibration standard concentrations: Back calculated calibration curve data for 5-ISMN are shown in Table IV-B-3. Data are acceptable.

Table IV-B-3. Back Calculated Calibration Curves
5-ISMN

Nominal Conc, ng/mL	N	%Nominal	%CV
7.99	15	97.1	11.3
15.98	14	99.2	10.0
29.97	15	103.3	6.0
89.91	15	101.3	10.7
299.7	15	98.6	4.0
449.55	15	100.2	5.1
539.46	14	100.7	6.1
599.4	15	99.7	5.8

b. Quality control samples: Precision and accuracy for the QC samples are shown in Table IV-B-4. Data are acceptable.

Table IV-B-4. Precision and Accuracy for QC Samples

Nominal Conc, ng/mL	N	%Nominal	%CV
20.14	30	109.2	10.3
201.40	30	106.4	7.7
483.36	30	106.1	6.3

V. Study Results: PK and Statistical Analyses

A. Study under fasting conditions

Subjects:

Of the 26 healthy, non-smoking, adult male volunteers who enrolled in the study, one did not complete the crossover.

Subject No. 1 elected to withdraw from the study 13.6 days after Period 1 dosing due to his job. Thus, a total of 25 subjects completed the study.

Deviations:

In Period 1, 17 of the 26 subjects had their 30-hour blood draw performed early (no more than 2 hours). As a result, in Period 2, the 30-hour scheduled sampling times for these subjects were modified to reflect the lagtime in Period 1.

Medical Events:

Subject No.8 fainted after blood draw of pre-dose sample. The medical Designate judged Subject No. 8 eligible for dosing. There were a total of 33 medical events (under test product: 16 events for 9 subjects; under reference product: 17 events for 10 subjects) such as headache, dizziness, nausea, etc. No serious medical events were reported during the study and no medication was required for any event.

Evaluation of study data: Reviewer recalculated all the pharmacokinetic parameters using reported elimination rate constants by the firm and statistics and the results of the recalculation are in agreement with the sponsor's submission.

Plasma 5-ISMN levels: Mean plasma 5-ISMN levels-time profiles are shown in Table V-A-1 and Fig. P-1. The test and reference products show comparable plasma concentration-time profiles.

PK parameters: Arithmetic and geometric means for AUCT, AUCI and CMAX for the test and reference products are shown in Table V-A-2. The 90% confidence intervals for the log-transformed AUCT, AUCI and CMAX, as shown in Table V-A-3, are all within the acceptable range of 80-125%.

There was no sequence effect for the log-transformed AUCT, AUCI or CMAX.

TABLE V-A-1: MEAN PLASMA 5-ISMN LEVELS FOR TEST AND REFERENCE PRODUCTS
UNDER FASTING CONDITIONS (N=25)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO

SD=STANDARD DEVIATION

Test Lot #K-20844; Ref Lot #23743

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	
0.167	35.77	74.74	96.86	121.97	0.37
0.25	112.42	123.02	179.07	144.79	0.63
0.33	224.34	166.10	253.39	149.40	0.89
0.5	325.09	123.59	322.54	131.66	1.01
0.75	371.78	89.92	347.60	91.53	1.07
1	358.14	66.07	348.65	73.91	1.03
1.25	350.07	65.22	347.16	70.64	1.01
1.5	341.74	49.10	341.56	59.86	1.00
2	328.55	55.11	324.39	47.83	1.01
2.5	308.31	51.20	319.89	50.13	0.96
3	288.31	43.10	279.29	39.55	1.03
4	252.50	46.27	266.39	53.53	0.95
6	190.15	40.21	191.77	35.70	0.99
8	145.33	31.97	147.25	31.14	0.99
12	83.76	18.40	83.91	16.56	1.00
16	52.90	15.46	53.56	14.74	0.99
24	16.04	5.38	17.82	10.45	0.90
30	4.34	5.47	3.19	5.02	1.36

TABLE V-A-2. ARITHMETIC/GEOMETRIC MEANS AND RATIOS
UNDER FASTING CONDITIONS for 5-ISMN (N=25)

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG

MEAN1=TEST; MEAN2=REFERENCE; RMEAN12=MEAN1/MEAN2 RATIO

SD=STANDARD DEVIATION

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	3078.92	555.03	3151.44	586.33	0.98
AUCT	2981.60	547.93	3016.84	517.38	0.99
CMAX	426.14	89.79	402.15	84.87	1.06
KE	0.14	0.01	0.14	0.02	1.00
LAUCI	3031.38	0.18	3101.97	0.18	0.98
LAUCT	2933.69	0.18	2974.60	0.17	0.99
LCMAX	417.61	0.20	394.21	0.20	1.06
THALF	5.10	0.49	5.17	0.97	0.99
TMAX	0.93	0.51	1.19	0.82	0.78

TABLE V-A-3. LSMEANS AND 90% CONFIDENCE INTERVALS
 UNDER FASTING CONDITIONS for 5-ISMN (N=25)
 UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
 LSM1=TEST; LSM2=REFERENCE; RLSM12=LSM1/LSM2 RATIO
 LOWCI12=LOWER 90% CI; UPPCI12=UPPER 90% CI

PARAMETER	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	3027.12	3097.80	0.98	93.93	101.66
LAUCT	2929.73	2971.15	0.99	94.52	102.87
LCMAX	417.35	393.14	1.06	97.30	115.82

B. Study under fasting/nonfasting conditions

Subjects:

Of the 18 healthy, non-smoking, adult male subjects who enrolled in the study, four did not complete the crossover. The Medical Designate withdrew Subjects No. 4 and 6 from the study after the 30-hour blood draw in Period 2 due to headache, nausea and vomiting. Subject No. 12 elected to withdraw from the study 6.2 days after Period 2 dosing (subject called to report he felt too sick to return for Period 3). Subject No. 16 was withdrawn from the study due to a positive urine drug screen result (cocaine) at Period 3 check-in. Thus, a total of 14 subjects completed the study. However, Subjects No. 6 and 12 were included in the pharmacokinetic and statistical evaluations since the two subjects completed the regimen 2 (test product-food) and regimen 3 (reference product-food).

Medical Events:

Subjects No. 4 and 6 were withdrawn from the study after the 30-hour blood draw in Period 2 due to headache, nausea and vomiting. There were a total of 73 medical events (under test product-fasting regimen: 28 events for 7 subjects; under test product-food regimen: 23 events for 7 subjects; under reference product-food regimen: 22 events for 9 subjects) such as headache, dizziness, nausea, etc. No serious medical events were reported during the study.

Evaluation of study data: Reviewer recalculated all the

pharmacokinetic parameters using reported elimination rate constants by the firm and statistics and the results of the recalculation are in agreement with the sponsor's submission. Numbers of subjects used in the data analyses were 14 for regimen 1 and 16 for regimens 2 and 3, respectively.

Plasma 5-ISMN levels: Mean plasma 5-ISMN levels-time profiles are shown in Table V-B-1 and Fig. P-2. The test and reference products show comparable plasma concentration-time profiles under nonfasting conditions. The test product under fasting conditions showed approximately 20% higher mean peak concentration than the test or reference product under nonfasting conditions.

PK parameters: Arithmetic and geometric means for AUCT, AUCI and CMAX for the test and reference products are shown in Table V-B-2. The data in Table V-B-2 show that food affects the CMAX (rate of absorption) but not the AUC (extent of absorption). Log of LSMEANS (as antilog) and the test/reference ratios under nonfasting conditions (designated as RLSM23) are shown in Table V-B-3. The test/reference ratios (RLSM23) are within the acceptable range of 0.8-1.25.

There was no sequence effect for the log-transformed AUCT, AUCI or CMAX.

TABLE V-B-1: MEAN PLASMA 5-ISMN LEVELS FOR TEST AND REFERENCE PRODUCTS
UNDER FASTING/NONFASTING CONDITIONS (N=16)

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REF-FOOD; RMEAN23=MEAN2/MEAN3 RATIO
SD=STANDARD DEVIATION

Test Lot #K-20844; Ref Lot #23743

TIME HR	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
0	0.00	0.00	0.00	0.00	0.00	0.00
0.167	22.71	24.66	1.83	5.00	15.57	23.91
0.25	112.50	153.68	14.74	17.18	50.32	63.46
0.33	205.92	171.82	36.77	41.82	69.07	69.97
0.5	343.97	172.89	83.76	80.02	129.24	103.13
0.75	366.72	98.79	142.54	96.61	198.94	115.17
1	352.59	75.11	199.00	116.43	249.63	116.76
1.25	327.63	60.80	226.21	113.63	269.95	123.90
1.5	311.70	47.14	261.20	87.55	272.63	94.81
2	300.10	35.78	306.60	58.39	285.86	51.64
2.5	290.15	49.39	301.80	53.49	277.65	40.33
3	259.20	40.97	274.19	40.83	270.62	40.49
4	233.48	28.16	251.85	36.10	244.89	36.30
6	181.90	24.15	190.44	31.26	191.47	28.88
8	136.07	21.48	146.83	23.31	151.23	34.29
12	80.36	16.63	80.34	15.52	81.35	12.72
16	43.28	8.59	46.51	7.99	45.39	10.45
24	15.53	4.06	15.61	3.54	15.77	4.94
30	2.01	4.00	3.13	4.88	1.59	4.35

(CONTINUED)

TIME HR	RMEAN12	RMEAN13	RMEAN23
0	.	.	.
0.167	12.43	1.46	0.12
0.25	7.63	2.24	0.29
0.33	5.60	2.98	0.53
0.5	4.11	2.66	0.65
0.75	2.57	1.84	0.72
1	1.77	1.41	0.80
1.25	1.45	1.21	0.84
1.5	1.19	1.14	0.96
2	0.98	1.05	1.07
2.5	0.96	1.05	1.09
3	0.95	0.96	1.01
4	0.93	0.95	1.03
6	0.96	0.95	0.99
8	0.93	0.90	0.97
12	1.00	0.99	0.99
16	0.93	0.95	1.02
24	1.00	0.99	0.99
30	0.64	1.26	1.96

TABLE V-B-2. ARITHMETIC/GEOMETRIC MEANS AND RATIOS
 UNDER FASTING/NONFASTING CONDITIONS for 5-ISMN (N=16)
 UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
 MEAN1=TEST-FAST; MEAN2=TEST-FOOD; MEAN3=REF-FOOD; RMEAN23=MEAN2/MEAN3 RATIO
 SD=STANDARD DEVIATION

PARAMETER	MEAN1	SD1	MEAN2	SD2	MEAN3	SD3
AUCI	2861.50	317.41	2755.69	313.21	2792.31	354.47
AUCT	2762.57	317.25	2662.38	312.72	2687.25	345.75
CMAX	430.45	118.08	339.95	34.39	329.67	67.02
KE	0.14	0.02	0.14	0.01	0.14	0.02
LAUCI	2845.40	0.11	2739.54	0.11	2770.99	0.13
LAUCT	2746.11	0.11	2645.71	0.12	2666.25	0.13
LCMAX	416.30	0.27	338.38	0.10	323.49	0.20
THALF	5.15	0.67	5.06	0.57	5.03	0.67
TMAX	0.95	0.44	1.93	0.73	1.85	0.93

(CONTINUED)

PARAMETER	RMEAN12	RMEAN13	RMEAN23
AUCI	1.04	1.02	0.99
AUCT	1.04	1.03	0.99
CMAX	1.27	1.31	1.03
KE	0.99	0.98	0.99
LAUCI	1.04	1.03	0.99
LAUCT	1.04	1.03	0.99
LCMAX	1.23	1.29	1.05
THALF	1.02	1.02	1.01
TMAX	0.49	0.51	1.04

TABLE V-B-3. LSMEANS UNDER FASTING/NONFASTING CONDITIONS for 5-ISMN (N=25)
 UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
 LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG
 LSM1=TEST-FAST; LSM2=TEST-FOOD; LSM3=REF-FOOD; RLSM23=LSM2/LSM3 RATIO

PARAMETER	LSM1	LSM2	LSM3	RLSM12	RLSM13	RLSM23
LAUCI	2884.30	2730.99	2766.16	1.06	1.04	0.99
LAUCT	2786.22	2638.22	2662.64	1.06	1.05	0.99
LCMAX	421.29	338.22	323.58	1.25	1.30	1.05

VI. Product Information and in vitro Testing

1. Formulation

Test formulation is shown in Table VI-1. The reference product, Schwarz's Monoket[®] Tablets, contains as inactive ingredients: lactose, talc, colloidal silicon dioxide, starch, microcrystalline cellulose and aluminum stearate.

Table VI-1. Test Formulation
 Teva's Isosorbide Mononitrate Tablets, 20 mg

Ingredients	Amount (mg)/Tablet
Isosorbide-5-Mononitrate	20
Lactose	
Microcrystalline Cellulose	
Sodium Starch Glycolate	
Povidone USP	
Magnesium Stearate	
Total Weight	

2. Assay and Content Uniformity Data

Assay and content uniformity data for the test and reference

products are shown in Table VI-2.

Table VI-2. Assay and Content Uniformity

Product	Assay, %	Content Uniform ity % (%CV)
Teva's Isosorbide Mononitrate Tablets, 20 mg Lot #K-20844 Batch size= . tablets	100.0	99.8 (1.3)
Schwarz's Monoket ^R Tablets, 20 mg Lot #23743 Exp. Date: Nov 2000	100.0	99.8 (1.9)

3. Dissolution Testing

Teva used its own dissolution method as shown in Table VI-3. The differences between Teva's method and FDA method were that Teva used 500 mL of water instead of 900 mL and Teva monitored the dissolution up to 45 minutes. Teva's dissolution data for the test and reference products, however, met the FDA dissolution specifications for Isosorbide Mononitrate Tablets as summarized in Table VI-3. Teva is advised to modify its dissolution method to conform to the FDA method. The FDA dissolution specifications are shown below:

Medium and Volume	water; 900 mL
Apparatus and rpm	2 (paddle); 50 rpm
Time	15 minutes
Tolerances	NLT in 15 minutes

VII. Summary and Comments

1. Pharmacokinetic and statistical evaluation:

A. Study under Fasting Conditions

Of the 26 healthy, non-smoking, adult male volunteers who enrolled in the study, one did not complete the crossover. Subject No. 1 elected to withdraw from the study 13.6 days after Period 1 dosing due to his job. Thus, a total of 25 subjects completed the study and used for the data analyses.

For the log-transformed AUCT, AUCI and CMAX for plasma 5-ISMN, the LSMEANS are comparable for the test and reference products and the 90% confidence intervals are within the acceptable range of 80-125%. The plasma 5-ISMN-time profiles for the test and reference products were comparable.

B. Study under Nonfasting Conditions

Sixteen of 18 subjects enrolled in the study were used in the data analyses. The test/reference ratios for log-transformed AUCT, AUCI, and CMAX for 5-ISMN under nonfasting conditions were within acceptable range of 0.8-1.25.

2. Bioanalytical method validation: Pre-study and within-study validation data are acceptable for the fasting and nonfasting studies.
3. Dissolution testing: Dissolution testing data on the test and reference products met the FDA specifications. However, the firm should change the volume of water from 500 mL to 900 mL and the dissolution time from 45 minutes to 15 minutes to conform to the FDA method.
4. Drug products: The assay and content uniformity data for the test and reference products are acceptable. The batch size of the test product was tablets.
5. Medical events: No serious medical events were reported during the two studies under fasting and nonfasting studies.

IV. Deficiency

None.

V. Recommendation

1. The two in vivo bioequivalence studies conducted under fasting and nonfasting conditions by Teva on its Isosorbide Mononitrate Tablets, 20 mg strength, lot #K-20844, comparing it to Schwarz's Monoket[®], 20 mg tablet, lot #23743, have been found acceptable. The studies demonstrate that Teva's Isosorbide Mononitrate Tablets, 20 mg strength, is bioequivalent to the reference product, Schwarz's Monoket[®], 20 mg tablet.
2. The dissolution testing conducted by Teva on its Isosorbide Mononitrate Tablets, 20 mg strength, lot #K-20844, is acceptable. However, the firm is advised to use the FDA dissolution method as described below.
3. The FDA dissolution testing should be incorporated into the firm's manufacturing controls and stability program. The dissolution testing should be conducted in 900 mL of water at 37°C using USP 23 Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specifications:

Not less than _____ of the labeled amount of the drug in the dosage form is dissolved in 15 minutes.

The firm should be informed of the recommendations.



Moo Park, Ph.D.
Chemist, Review Branch III
Division of Bioequivalence

RD INITIALED RMHATRE
FT INITIALED RMHATRE
Ramakant M. Mhatre, Ph.D.
Team Leader, Review Branch III
Division of Bioequivalence

Ramakant M. Mhatre

12/3/97

Concur: Rabindra Patnaik
Rabindra Patnaik, Ph.D.
Acting Director
Division of Bioequivalence

Date: 1/15/98

Table VI-3. In Vitro Dissolution Testing Data

I. General Information						
Drug Product (Generic Name)		Isosorbide Mononitrate Tablets				
Strength		20 mg				
ANDA Number		75-147				
Applicant		Teva				
Reference Drug Product		Schwarz's Monoket Tablets, 20 mg				
II. Teva's Method for Dissolution Testing						
Medium and Volume		water; 500 mL				
Apparatus and rpm		2 (paddle); 50 rpm				
Time		45 minutes				
Tolerances		NLT) in 45 minutes				
Assay Method						
III. Dissolution Data (%)						
Time	Test Product			Reference Product		
	Lot No:K-20844			Lot No:23743		
	Strength:20 mg			Strength:20 mg		
	No of Units:12			No of Units:12		
Min	Mean	Range	%CV	Mean	Range	%CV
15	98.3		1.5	100.7		1.6
30	100.6		1.1	100.6		1.5
45	101.1		1.1	100.5		1.3

FIG P-/. PLASMA ISOSORBIDE MONONITRATE LEVELS

ISOSORBIDE MONONITRATE TABLETS, 20 MG, ANDA #75-147

UNDER FASTING CONDITIONS

DOSE=1 X 20 MG

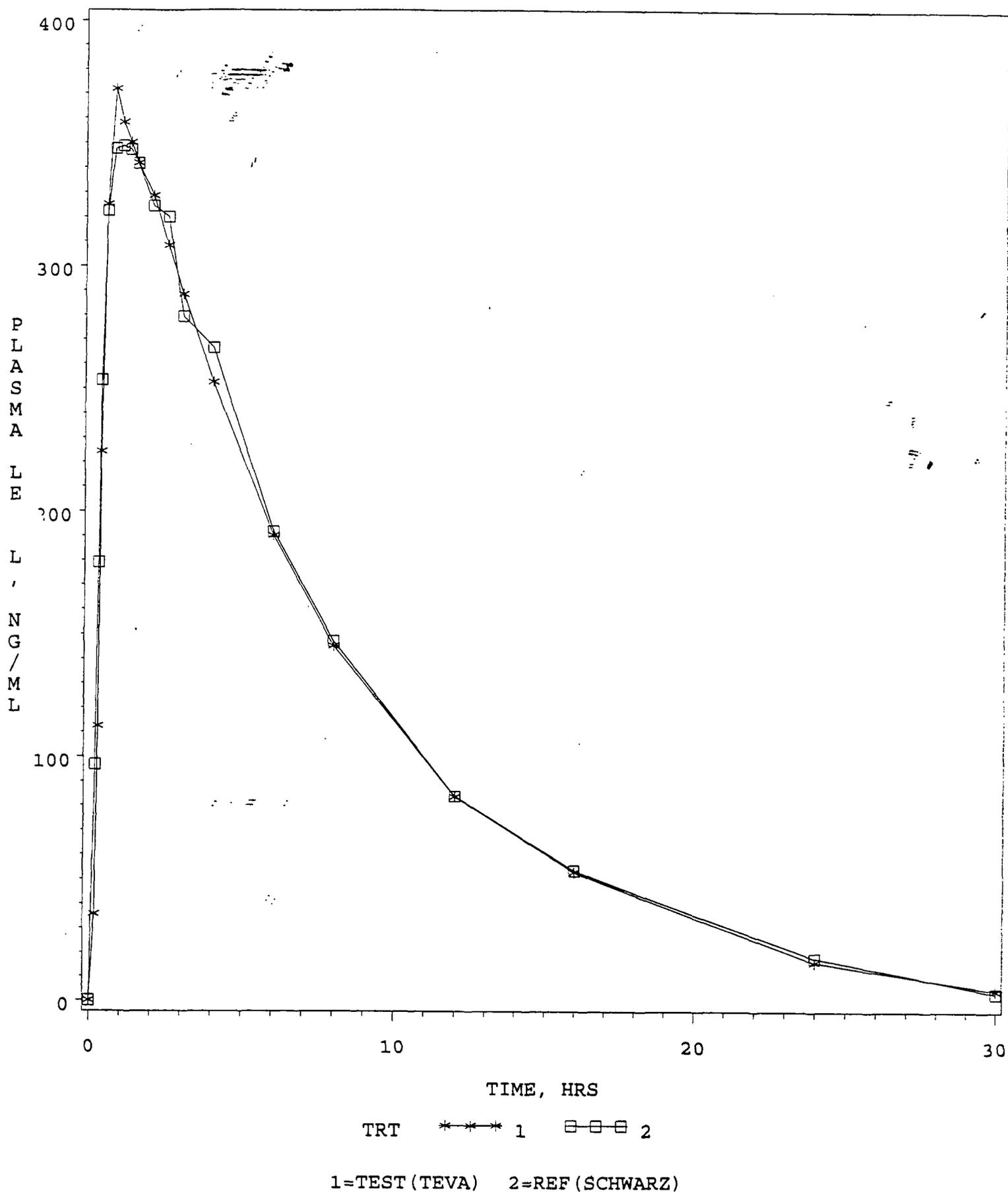


FIG P-2. PLASMA ISOSORBIDE MONONITRATE LEVELS

ISOSORBIDE MONONITRATE TABLETS, 20 MG, ANDA #75-147
UNDER FASTING/NONFASTING CONDITIONS
DOSE=1 X 20 MG

